[c.44C>T; p.(Thr15Met)] showed fatty atrophy of gastrocnemii with asymmetric myoedema involving the right gastrocnemius and negligible fatty atrophy of bilateral gluteus maximus and thigh muscles. The other patient with GFPT1 showed mild fatty infiltration of gluteal muscles, moderate symmetrical fatty infiltration involving gluteus maximus, quadriceps, adductor brevis and magnus. Two siblings with DPAGT1(homozygous, c.652C>T) showed mild fatty infiltration of gluteal muscles, moderate symmetrical fatty infiltration gluteus maximus. The distinctive MR imaging pattern, coupled with relatively slowly progressive fatigable limb-girdle weakness, would facilitate an early diagnosis of the milder form of CMS-CDG disorders that are more benign in nature. Thus MRI could aid in directing the accurate approach to genetic diagnosis as well as selection of therapy.

Keywords: Congenital myasthenic syndromes; Muscle magnetic resonance imaging, CMS-CDG disorders; GMPPB; DPAGT1; GFPT1

SS20.03

Efficacy of Efgartigimod in Generalized Myasthenia Gravis: Myasthenia Gravis Composite Score Analysis From ADAPT

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Introduction: Efgartigimod is a human IgG1 antibody Fc-fragment that blocks the neonatal Fc receptor and reduces IgG autoantibody levels. The safety and efficacy of efgartigimod was assessed in ADAPT, a 26-week, global, multicenter, phase 3, randomized, double-blind, placebo-controlled trial in patients with generalized myasthenia gravis (gMG). The Myasthenia Gravis Activities of Daily Living (MG-ADL) scale and Quantitative Myasthenia Gravis (QMG) scores were utilized as primary and secondary outcome measures, while the Myasthenia Gravis Composite (MGC) score was evaluated as an exploratory endpoint. The MGC comprises both physician-reported (muscle strength and ocular function) and patient-reported (talking, chewing, swallowing, and breathing) outcomes. MGC response options are weighted and were developed using the highest performing items from preexisting MG-specific scales. Total scores range from 0-50, with higher scores indicating more severe symptoms. Based on published literature, a 3-point improvement in score is considered clinically meaningful. Previously reported data have shown that a significantly greater proportion of efgartigimod-treated patients achieved clinically meaningful improvement (CMI) in MG-ADL and QMG scores compared to placebo-treated patients. The goal of the current analysis is to evaluate the efficacy of efgartigimod using the MGC, which was assessed during the ADAPT study.

Methods: Patients were randomized to receive efgartigimod (n=84) or placebo (n=83). A subset of patients were anti-acetylcholine receptor (AChR) antibody positive (n=65 efgartigimod versus n=64 placebo). Efgartigimod 10 mg/kg was administered intravenously in cycles of once-weekly infusions for 4 weeks, with subsequent cycles initiated based on clinical evaluation. Mean MGC change from baseline was a predefined exploratory endpoint.

Results: The mean (SE) reduction in MGC score at week 4 was -8.913 (0.974) for efgartigimod-treated anti-AChR antibody positive patients during cycle 1 compared with -2.871 (1.007) for placebo-treated patients (95% CI, -8.181 to -3.904; P<.0001). A similar improvement was seen in the overall population, with a mean (SE) change of -9.231 (0.878) in the efgartigimod group and -4.497 (0.885) in the placebo group (95% CI, -6.668 to -2.800; P<.0001). Similar results occurred during subsequent treatment cycles in both populations. A

CMI of ≥3 points was observed in 81.0% of anti-AChR antibody positive patients in the efgartigimod group compared to 60.0% in the placebo group at week 4, with improvements reaching ≥10 points in 47.6% of patients in the efgartigimod group and 8.3% in the placebo group. In the overall population at week 4, 82.5% (efgartigimod) versus 63.3% (placebo) achieved a ≥3-point improvement, with improvements reaching ≥10 points in 46.3% (efgartigimod) and 12.7% (placebo) of patients. The most frequently observed adverse events are described below. Headache occurred with similar frequency between treatment groups. Nasopharyngitis, nausea, and diarrhea were more frequent in placebo patients. Upper respiratory tract infections and urinary tract infections occurred more in efgartigimod-treated patients. Adverse events were predominantly mild or moderate.

Conclusions: In the ADAPT study, efgartigimod treatment resulted in greater mean reductions of MGC scores (a composite measure incorporating both physician- and patient-reported outcomes) compared to placebo. The current analysis adds to the existing data that show efgartigimod is a promising new treatment for patients with gMG.

SS21.01

The Interface of Neuromuscular Transmission and Mitochondrial Diseases

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Mutations in either the mitochondrial or nuclear genomes are associated with a diverse group of human disorders characterized by impaired mitochondrial respiration. The clinical presentation of mitochondrial diseases is very variable, and there are only very few effective treatments to date.

Within this group of diseases, an increasing number of mutations have been identified to cause a defect of neuromuscular junction which can be treated with drugs improving neuromuscular transmission. The fatigable weakness in these conditions may improve on therapy.

The overall prevalence of neuromuscular transmission defects in mitochondrial diseases is about 25%. Patients with some selected gene defects have been shown more frequently to present with a defect of the neuromuscular transmission, such as pathogenic dominant RRM2B variants or specific recessive variants in SLC25A1 and TEFM. The use of drugs improving the neuromuscular transmission may be beneficial in some of these patients.

The presentation will give an overview on mitochondrial diseases with neuromuscular transmission defects and will provide some guide to the diagnosis and treatment of these diseases.

SS21.02

New Synaptic and Presynaptic Defects of the Neuromuscular Junction

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Congenital myasthenic syndromes (CMS) are a heterogenous group of disorders caused by my mutations in genes encoding proteins that are essential for neuromuscular transmission. Next-generation sequencing (NGS) technology has helped to expand the genetic landscape of CMS with more than 30 subtypes described to date. The most common classification of CMS relies on the location of the mutated protein into presynaptic, synaptic or postsynaptic CMS and those thar are ubiquitously expressed. Postsynaptic CMS is by far the most common subtype of CMS accounting for approximately 70-80% of cases, but presynaptic and synaptic CMS are gaining attention as we improve our understanding on the function and molecular organization of the neuromuscular synapse. Until recently, mutations in the choline acetyltransferase gene (CHAT) were the only cause of presynaptic CMS described, but in recent years the landscape of presynaptic CMS genes has greatly expanded with the discovery of CMS genes involved in axonal transport (MYO9), synthesis and recycling of acetylcholine (SLC5A7, SLC18A3, PREPL) and vesicle exocytosis (SYT2, VAMP1, SNAP25B, UNC13A). Presynaptic CMS are generally rare and may present with central manifestations such as intellectual disability or learning difficulties derived from the expression of the mutated protein beyond the neuromuscular junction (NMJ), challenging the original definition of CMS. Other key clinical features include early onset, severe disease, respiratory